REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1-15 are amended herein to address issues of claim format, grammar and spelling. Claim 27 is canceled herein. Applicants reserve the right to file a continuation or divisional application directed to any subject matter deleted by way of this Amendment. No new matter is submitted by way of this Amendment, as basis for the amendments to the claims and specification may be found throughout the specification and claims as-filed.

Objections to Specification

The use of the trademarks COMPLETE™ and MULTIPHOR ™ have been noted in this application. The specification has been amended herein to capitalize the trademarks. Applicants also provide herein two references supporting the assertion that these two trademarks and their generic contents were well known in the art: "Protease Inhibitor Cocktail Tablets" product description from Roche Diagnostics GmbH, and "Protein Electrophoresis technical manual" prepared by Amersham Biosciences.

The specification is objected to as it purportedly contains primer sequences more than four amino acids in length and fail to recite sequence identifiers. The paper copy of the Sequence Listing for the subject application, is by this

Amendment, added after the last page of the application to replace the Sequence Listing previously filed on May 28, 2003. The specification is further amended to recite appropriate sequence identifiers. Thus, Applicants respectfully submit that the objection has been overcome.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-20 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regard as the invention.

Claims 1-15 are purportedly missing an article at the beginning of the claims. The claims have been amended herein to add an article to the beginning of the claims. Thus, this rejection is obviated. Claim 4 stands rejected for the recitation of the phrase "purified from human skin," as the source of the skin is purportedly unclear. Applicants note that the polypeptide may also be obtained from a sample obtained from a human (non-cultured) epidermis, as set forth in Example 1 of the present specification. To this end, claim 4 is amended herein to recite purification for cultured and non-cultured human skin.

Claim 6 stands rejected for the recitation of "in part comprises", as the term "comprises" purportedly already reads on a sequence having all the amino acids of SEQ ID NO: 1 and with or without any additional amino acids. Claim 6 has been amended herein to recite "consisting of". Thus, this rejection is obviated

Claims 7 and 8 stand rejected as purportedly indefinite for the recitation of the phrases "theoretical isoelectric point" and "theoretical molecular weight". As noted on pages 7 and 8 of the specification, the theoretical isoelectric point is derived from the amino acid scheme of the peptide chain, rather than any type of physical measurement such as isoelectric focusing. Theoretical molecular weight is similarly the result of analysis of the amino acid scheme of the polypeptide, rather than the apparent molecular weight as may be measured by comparing electrophoretic mobility of a peptide to that of a known standard protein chain. Thus, the skilled artisan would know what is meant by these phrases.

Claims 10-14, 17, 18, and 25 stand rejected as purportedly indefinite for the recitation of the phrase "at least one". Applicants submit that the use of "at least one" as used in claim 10 refers to calcium binding sites, rather than polypeptides. Basis for this assertion may be found throughout the specification. Also, Applicants note that claim 11 neither contains nor is dependant upon any claim containing the phrase "at least one." With regard to the other rejected claims, claim 1 is directed towards "purified or natural polypeptides comprising amino acid sequence SEQ ID NO: 1." Thus, use of the term "comprises" refers to any polypeptide chain containing the sequence disclosed in claim 1, but does not limit the polypeptide to that sequence alone. Claims 13, 14, 17, 18, and 25 are directed to a polypeptide containing "at least one" of the many such claimed polypeptide chains of claim 1.

Claim 11 stands rejected as indefinite because it is purportedly unclear as to what is fixed by the calcium. Applicants submit that calcium is "fixing" to the claimed polypeptide, rather than being fixed to another molecule. The specification recites that the purpose of calcium binding (or fixing) is to induce a conformation change in the claimed polypeptide which allows it to act in a regulatory manner in an environment of changing calcium concentration.

Claims 17 and 18 stand rejected as indefinite for the recitation of the term "transglutaminases" because it is purportedly unclear as to which transglutaminases are claimed. Applicants submit that the specific transglutaminases in questions would be clear to the skilled artisan, based on what is stated in the specification. For example, Applicants note that pages 12-13 of the specification refer to transglutaminases such as transglutaminase 3.

Claims 17 and 18 also stand rejected for the recitation of the phrase "to a patient in need of such regulation" because it is purportedly unclear as to how one would diagnose this need. Applicants submit that, as noted throughout the instant specification, transglutaminase is instrumental in the formation of corneal casings. Problems or genetic mutations in the production pathway of transglutaminase can cause a number of clinically manifested diseases, notably lamellar ichthyosis. Applicants submit that the diagnosis of this and other transglutaminase-related disorders and subsequent treatment using the polypeptide disclosed herein would be known by a physician, dermatologist, or anyone skilled in the art, given the clinically manifested symptoms of such disorders.

Claims 16 and 20 stand rejected as indefinite for the recitation of the term "neoplasia" as the term is purportedly unclear. Applicants submit that this term would be understood by the skilled artisan because the specification lists neoplasia as an "impairment of epidermal proliferation or differentiation," (page 11, line 12). Thus, it would be clear to one skilled in the art that "neoplasia" denotes an epidermal skin tumor.

Claim 12 stands rejected as indefinite for the recitation of the phrase "effective amount" because it is purportedly unclear what the effective amount is for. Claim 12 has been amended herein to recite "amount effective to regulate the impairments of normal or pathological epidermal proliferation or differentiation". Thus, this rejection is obviated.

Claim 13 stands rejected for the recitation of the phrase "intended to regulate the impairments of epidermal, normal or pathological proliferation or differentiation, comprising..." as purportedly indefinite because "epidermal "is an adjective. Claim 13 is amended herein to recite "normal or pathological epidermal proliferation or differentiation." This clarifies that claim 13 is directed towards the normal and pathological proliferation and differentiation of the epidermis. Thus, this rejection is obviated.

Objections to Claims

Claim 10 is objected to as purportedly containing an additional "in" and for purportedly misspelling the word "one". Claim 10 has been amended herein to address these issues of grammar and spelling. Thus, the objection is obviated.

Rejections under 35 U.S.C. § 101

Claim 6 stands rejected under 35 U.S.C. § 101 as purportedly lacking utility. The Office Action states that the invention of claim 6 as directed to a "natural . . . polypeptide whose sequence in part comprises the sequence of the polypeptide as described in claim 1" is found occurring in nature in the skin of animals. Claim 6 has been amended herein to remove "natural". Thus, this rejection is obviated.

Rejections under 35 U.S.C. § 102

Claim 28 stands rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Flavell *et al.* (U.S. Patent No. 5,747,294). Flavell *et al.* purportedly disclose a recombinant protein that is obtained by expression of an expression vector pGex-2T that contains part of the sequence that codes SEQ ID NO: 2. The Office Action states that all of the elements of claim 28 are anticipated by Flavell *et al.* Applicants traverse.

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253, 256 (Fed. Cir.

1985). Applicants submit that the cited reference does not anticipate the claimed invention. Flavell *et al.* do not disclose the entire sequence of SEQ ID NO: 2 and therefore the reference does not contain all of the elements of present claim 28.

Claims 6 and 27 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Hillman *et al.* (U.S. Patent No. 6,046,315). Hillman *et al.* purportedly disclose a recombinant DACP-1 which has an amino acid sequence with 99.6% identity to SEQ ID NO: 1. The Examiner argues that Hillman *et al.* purportedly disclose a recombinant protein that corresponds to part of SEQ ID NO: 1. The Office Action states that all of the elements of claims 6 and 27 are disclosed by Hillman *et al.* Applicants traverse.

Claim 6 is amended herein to recite the sequence of claim 1. This sequence is not disclosed by the cited reference, and thus Applicants submit this claim is not anticipated by the cited reference. Claim 27 is canceled herein.

Thus, Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

Rejections under 35 U.S.C. § 103

Claim 9 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Hillman *et al.* Hillman *et al.* purportedly disclose a sequence with 99.6% sequence similarity to SEQ ID NO: 1 and fragments thereof which are useful in treating disorders. The Office Action states that it would have been obvious to

one of ordinary skill in the art at the time of the invention to use Kex 1 and Kex 2 for proteolysis of the Hillman *et al.* sequence into fragments, which would cleave the peptide at the "KK" and "RK" positions, resulting in a mixture of polypeptides that could be the same as a "mixture of polypeptides obtained from the proteolysis of the polypeptide" of SEQ ID NO: 1. Applicants traverse.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action. Hillman *et al.* fail to provide any suggestion or motivation to cleave the polypeptide of Hillman to obtain the fragments of the polypeptide of SEQ ID NO 1. As SEQ ID NO:1 was not known to the skilled artisan, there is no disclosure or suggestion of cleaving the sequence of SEQ ID NO:1.

As the cited reference does not provide a suggestion or motivation to modify the reference to arrive at the claimed invention, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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